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Systematic Review

Unlocking Early Neural Plasticity: A Systematic Review and Meta-Analysis of Repetitive Transcranial Magnetic Stimulation on Motor Recovery in Acute Stroke

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) has demonstrated efficacy as a neuromodulatory technique in subacute and chronic stroke phases. However, evidence regarding its effectiveness in the acute phase remains limited, necessitating further synthesis and evaluation. **Methods:** A comprehensive search was conducted across PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL (EBSCOhost) to November 1, 2025. The intervention in the experimental group must involve rTMS with or without any additional rehabilitation. Using a random-effects model, standardized mean differences (Hedges' g) were calculated for motor function (Fugl-Meyer Assessment, FMA), neurological deficits (National Institutes of Health Stroke Scale, NIHSS), independence (Barthel Index, BI), disability (Modified Rankin Scale, mRS), grip strength, and neurophysiological parameters (Motor Evoked Potential (MEP) amplitude, resting motor threshold (RMT), Central Motor Conduction Time (CMCT)). Heterogeneity was assessed using the I^2 statistic, and analyses were conducted with Stata. **Results:** A systematic literature search identified 17 studies meeting the inclusion criteria involving 846 acute ischemic stroke adults. rTMS significantly improved motor recovery (FMA: $p < 0.01$) and reduced neurological deficits (NIHSS: $p < 0.01$). It also enhanced independence (BI: $p = 0.01$) and reduced disability (mRS: $p < 0.01$; grip strength: $p = 0.01$). Neurophysiological outcomes indicated increased corticospinal excitability in the lesioned hemisphere (MEP amplitude: $p < 0.01$) and reduced RMT ($p < 0.01$), with no significant effect on CMCT. Subgroup analyses showed comparable benefits between ipsilesional high-frequency and contralesional low-frequency rTMS, though high-frequency protocols yielded significant improvements in activities of daily living ($p = 0.01$). Subthreshold stimulation and threshold stimulation were associated with NIHSS improvements ($p < 0.01$). Suprathreshold stimulation showed a non-significant effect ($p = 0.11$). **Conclusions:** Despite heterogeneity and limitations in evidence quality, rTMS shows promise as a neurorehabilitative intervention in acute stroke, potentially by modulating interhemispheric balance and promoting neuroplasticity.

Keywords: stroke; repetitive transcranial magnetic stimulation; motor function; rehabilitation; meta-analysis

1. Introduction

Stroke is a prevalent neurological disorder with high mortality and disability rate [1]. Motor dysfunction represents the most common neurological deficit post-stroke, with approximately 80% of survivors experiencing upper limb impairment [2,3]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, safe, and effective neurorehabilitation technology that modulates cortical excitability through rapidly changing magnetic fields, commonly used to promote functional reorganization in stroke patients by stimulating synaptic plasticity and regulating cortical excitability [4,5,6]. High-frequency (HF) rTMS is typically applied to the affected hemisphere to enhance neural excitability in damaged regions, or low-frequency (LF) stimulation is applied to the unaffected hemisphere to reduce abnormally high interhemispheric inhibition that occurs post-stroke [7,8].

Previous studies have proposed the concept of an early critical time window for rehabilitation, suggesting that earlier effective rehabilitation intervention yields greater recovery benefits [9]. Most new therapies (such as non-invasive brain stimulation, robot-assisted training, etc.) have their efficacy evidence derived from studies on patients in the chronic phase, while they are recommended

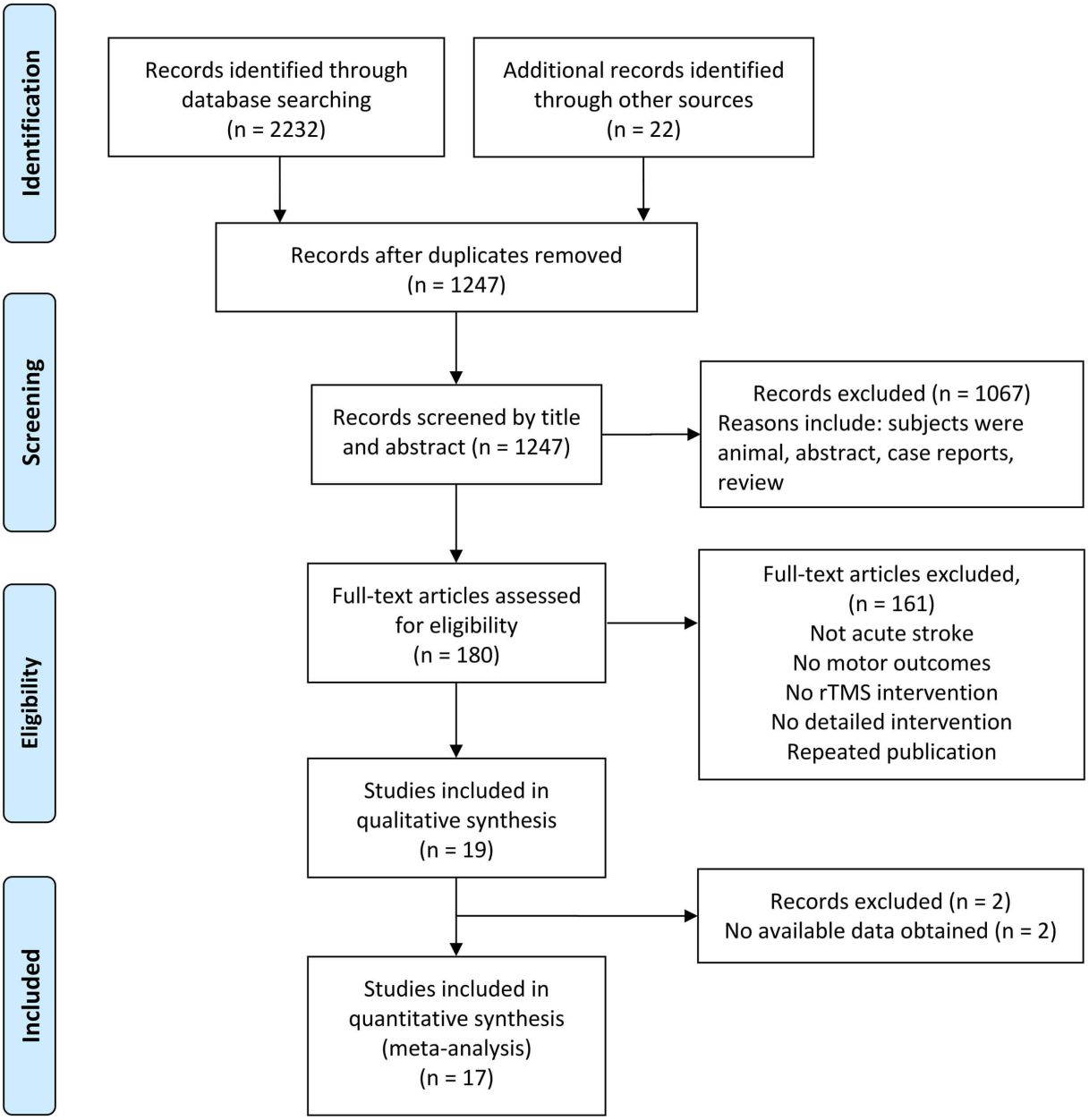

Fig. 1. PRISMA flowchart of the search process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; rTMS, repetitive transcranial magnetic stimulation.

for use in early rehabilitation, there is a lack of adequate validation from studies conducted specifically within that corresponding early time window [10,11]. Recent meta-analytic evidence that specifically addresses motor recovery in the acute/sub-acute phase, which found that non-invasive brain stimulation (including rTMS) combined with other therapies effectively improved upper extremity motor function (measured by Fugl-Meyer Assessment Upper Extremity, FMA-UE) in acute/sub-acute stroke patients, but not in chronic stroke patients [12]. However, the study highlights the efficacy in the broader acute/sub-acute window (<6 months), their analysis did not specifically isolate or explore the effects of rTMS in the early (within 1 week) acute period. Therefore, conducting a further meta-analysis specifically focusing on clinical trials involving acute post-stroke patients is both necessary and meaningful.

To our knowledge, this is the first meta-analysis examining rTMS intervention for motor dysfunction in acute post-stroke patients. In our study, we conducted rigorous screening and meta-analysis of recent literature involving acute post-stroke patients, including quality assessment. Furthermore, we explored the differential effects of various rTMS parameters (including stimulation location and intensity) on overall motor function (using the Fugl-Meyer Assessment) in adults with acute stroke. We conducted exploratory analyses on both upper limb (Fugl-Meyer Assess-

Table 1. Characterization of included studies.

Study	Group	Age (years)	Gender (F/M)	Type of stroke	Stroke onset time (d)	rTMS intervention				Outcome extracted	Adverse events
						Location	Frequency	Intensity	Pulses		
Chen et al. 2021 [13]	Group 1: 1 Hz–10 Hz (n = 25) Group 2: sham-10 Hz (n = 25) Group 3: 1 Hz-sham (n = 25) Group 4: sham-sham (n = 25)	Group 1: 58.00 (44.50, 65.50) Group 2: 62.00 (49.00, 67.00) Group 3: 63.00 (43.00, 67.00) Group 4: 65.00 (52.00, 73.00)	Group 1: 7/17 Group 2: 7/18 Group 3: 8/17 Group 4: 7/18	ischemic stroke	Group 1: 7 (5.00, 10.00) Group 2: 5 (4.00, 9.00) Group 3: 7 (4.50, 11.50) Group 4: 5 (4.00, 9.50)	10 Hz over the ipsilesional M1; 1 Hz over the contralesional M1	Group 1: real 1 Hz + real 10 Hz Group 2: sham 1 Hz + real 10 Hz Group 3: real 1 Hz + sham 10 Hz Group 4: sham 1 Hz + sham 10 Hz	90% RMT	Group 1: 1200 Group 2: 600 Group 3: 600	FMA, FMA-UL, NIHSS, ADL(BI), mRS, MEP amplitude (nonlesioned/lesioned) RMT (nonlesioned/lesioned), CMCT (nonlesioned/lesioned)	No harmful events were found apart from 3 temporary headaches and 2 tingling feelings on the brain at the start of stimulation.
Guan et al. 2017 [14]	Group 1: real rTMS (n = 21) Group 2: sham rTMS (n = 21)	Group 1: 59.7 ± 6.8 Group 2: 57.4 ± 14.0	Group 1: 5/16 Group 2: 7/14	ischemic stroke	Group 1: 3.8 ± 3.4 Group 2: 4.8 ± 4.1	ipsilesional M1	5 Hz	120% RMT	1000	FMA-UL, FMA-LL, NIHSS, BI, mRS, RMT (lesioned)	None of the patients complained of discomfort after rTMS or sham rTMS.
Du et al. 2016 [15]	Group 1: 3-Hz rTMS (n = 23) Group 2: 1-Hz rTMS (n = 23) Group 3: control (n = 23)	Group 1: 56.78 ± 8.47 Group 2: 56.78 ± 12.4 Group 3: 53.61 ± 13.55	Group 1: 8/15 Group 2: 7/16 Group 3: 9/14	ischemic stroke	Group 1: 7 (4–16) Group 2: 6 (5–12) Group 3: 8 (3–24)	Group 1: ipsilesional hemisphere M1 Group 2: contralesional hemisphere M1	Group 1: 3 Hz Group 2: 1 Hz	Group 1: 80–90% RMT Group 2: 110–120% RMT	1200	FMA-UL, FMA-LL, NIHSS, BI, MEP amplitude (nonlesioned/lesioned) RMT (nonlesioned/lesioned)	No adverse effects were observed except for three transient headaches and one tingling sensation on the head at the beginning of the stimulation.
Du et al. 2016 [16]	Group 1: 3-Hz rTMS (n = 15) Group 2: 1-Hz rTMS (n = 13) Group 3: control (n = 12)	Group 1: 58.2 ± 2.78 Group 2: 57.92 ± 2.47 Group 3: 58.83 ± 3.35	Group 1: 2/13 Group 2: 6/7 Group 3: 6/6	ischemic stroke	Group 1: 8 (4–15) Group 2: 6 (5–28.5) Group 3: 9 (7–26.25)	Group 1: ipsilesional M1 Group 2: contralesional M1	Group 1: 3 Hz Group 2: 1 Hz	Group 1: 90% RMT Group 2: 100% RMT	1200	mRS	Three patients (two active rTMS and one control) experienced transient headache and one patient (active rTMS) experienced a tingling sensation inthe head following the first rTMS session.
Du et al. 2019 [17]	Group 1: HF-rTMS (n = 20) Group 2: LF-rTMS (n = 20) Group 3: sham (n = 20)	Group 1: 54 ± 12 Group 2: 56 ± 9 Group 3: 56 ± 11	Group 1: 6/14 Group 2: 2/18 Group 3: 4/16	ischemic stroke	Group 1: 5 ± 4 Group 2: 6 ± 4 Group 3: 4 ± 3	Group 1: ipsilesional M1 Group 2: contralesional hemisphere M1	Group 1: 10 Hz Group 2: 1 Hz	100% RMT	1200	FMA-UL, MEP amplitude (nonlesioned/lesioned), RMT (nonlesioned/lesioned), CMCT (nonlesioned/lesioned)	No adverse effects, except for two transient headaches at the beginning of stimulation.

Table 1. Continued.

Study	Group	Age (years)	Gender (F/M)	Type of stroke	Stroke onset time (d)	rTMS intervention				Outcome extracted	Adverse events
						Location	Frequency	Intensity	Pulses		
Du et al. 2022 [18]	Group 1: HF-rTMS (n = 15) Group 2: LF-rTMS (n = 17) Group 3: sham (n = 14)	Group 1: 51 ± 10 Group 2: 56 ± 10 Group 3: 52 ± 11	Group 1: 3/12 Group 2: 3/14 Group 3: 2/12	ischemic stroke	Group 1: 4 ± 4 Group 2: 4 ± 2 Group 3: 6 ± 4	Group 1: ipsilesional hemisphere M1 Group 2: contralesional hemisphere M1	Group 1: 10 Hz Group 2: 1 Hz	100% RMT	1200	FMA	-
Matsuura et al. 2015 [19]	Group 1: real rTMS (n = 10) Group 2: sham rTMS (n = 10)	Group 1: 72.2 ± 6.0 Group 2: 74.7 ± 12.7	Group 1: 4/6 Group 2: 5/5	ischemic stroke	Group 1: 9.4 ± 5.3 Group 2: 9.8 ± 2.8	Contralesional motor cortex	1 Hz	100% RMT	1200	FMA, Grip strength, MEP amplitude (non-lesioned/lesioned)	No any adverse effects.
Watanabe et al. 2018 [20]	Group 1: iTBS (n = 8) Group 2: 1-Hz rTMS (n = 7) Group 3: sham rTMS (n = 6)	Group 1: 72.5 (6.5) Group 2: 67.6 (6.4) Group 3: 75.2 (5.5)	Group 1: 3/5 Group 2: 1/6 Group 3: 3/3	ischemic stroke	within 7 days	Group 1: ipsilesional M1 Group 2: contralesional M1	Group 1: iTBS Group 2: 1 Hz	Group 1: 80% RMT Group 2: 110% RMT	Group 1: 600 Group 2: 1200	FMA, Grip strength, MEP amplitude (lesioned)	No patients had symptoms suggestive of seizure.
Khedr et al. 2005 [21]	Group 1: real rTMS (n = 26) Group 2: sham rTMS (n = 26)	Group 1: 53.5 ± 9.5 Group 2: 52.2 ± 8.4	Group 1: 7/19 Group 2: 9/17	ischemic stroke	Group 1: 7.1 ± 1.4 Group 2: 7.3 ± 1.5	ipsilesional hemisphere	3 Hz	120% RMT	300	NIHSS, BI	No side effects of rTMS except occasional mild headache.
Khedr et al. 2009 [22]	Group 1: real rTMS (n = 14) Group 2: sham rTMS (n = 12)	Group 1: 58.9 ± 11.7 Group 2: 56.2 ± 13.4	-	ischemic stroke	Between 5 and 10 days	Ipsilesional oesophageal cortical area	3 Hz	120% RMT	300	BI, Grip strength	-
Khedr et al. 2010 [23]	Group 1: 3 Hz-rTMS (n = 16) Group 2: 10 Hz-rTMS (n = 16) Group 3: sham (n = 16)	Group 1: 58.25 ± 15.07 Group 2: 58.37 ± 13.96 Group 3: 58 ± 11.64	Group 1: 8/8 Group 2: 9/7 Group 3: 7/9	ischemic stroke	Group 1: 8 ± 5.059 Group 2: 6 ± 2.82 Group 3: 6.2 ± 1.54	ipsilesional motor cortex	Group 1: 3 Hz Group 2: 10 Hz	Group 1: 130% RMT Group 2: 100% RMT	750	NIHSS, mRS, MEP amplitude (nonlesioned/lesioned) RMT (nonlesioned/lesioned)	Without any adverse effects.

Table 1. Continued.

Study	Group	Age (years)	Gender (F/M)	Type of stroke	Stroke onset time (d)	rTMS intervention				Outcome extracted	Adverse events
						Location	Frequency	Intensity	Pulses		
Komatsu et al. 2024 [24]	Group 1: rTMS + conventional rehabilitation (n = 39) Group 2: conventional rehabilitation (n = 39)	Group 1: 63 (55–72) Group 2: 66 (53–75)	Group 1: 9/30 Group 2: 10/29	ischemic stroke	Group 1: 3 (3–3) Group 2: 3 (3–3)	ipsilesional motor cortex	10 Hz	90–100% RMT	2400	NIHSS	No record any instances of epilepsy or exacerbation of NIHSS score.
Zhu et al. 2022 [25]	Group 1: rTMS (n = 50) Group 2: control (n = 50)	Group 1: 48.25 ± 12.82 Group 2: 48.13 ± 13.42	Group 1: 23/27 Group 2: 26/24	ischemic stroke	Group 1: 4.15 ± 1.82 Group 2: 4.23 ± 2.25	Left DLPFC	5 Hz	60% RMT	800	NIHSS	No striking difference in those side effects between the two groups.
Liepert et al. 2007 [26]	Group 1: real rTMS Group 2: placebo rTMS crossover trial, total n = 12	63 ± 11	4/8	stroke	7.3 ± 4.5	contralesional M1	1 Hz	90% RMT	1200	Grip strength	-
Guo et al. 2021 [27]	Group 1: HF-rTMS (n = 11) Group 2: LF-rTMS (n = 12) Group 3: sham (n = 10)	Group 1: 65.09 ± 5.84 Group 2: 63.58 ± 7.95 Group 3: 64.9 ± 6.23	Group 1: 6/5 Group 2: 7/5 Group 3: 5/5	ischemic stroke	Group 1: 6.00 ± 2.37 Group 2: 5.42 ± 1.93 Group 3: 5.1 ± 1.79	Group 1: ipsilesional M1 Group 2: contralesional M1	Group 1: 10 Hz Group 2: 1 Hz	90% RMT	Group 1: 1500 Group 2: 900	FMA, NIHSS, BI	No discomfort was reported.
Valovičová et al. 2024 [28]	Group 1: real rTMS (n = 13) Group 2: placebo rTMS (n = 13)	Group 1: 69.9 ± 14.0 Group 2: 74.6 ± 10.4	Group 1: 6/7 Group 2: 7/6	ischemic stroke	Group 1: 2 (1–6) Group 2: 3 (2–5)	ipsilesional motor cortex	10 Hz	100% RMT	1500	FMA-UL, FMA-LL, NIHSS, BI, MEP amplitude (nonlesioned/lesioned), CMCT (nonlesioned/lesioned)	-
Ma et al. 2024 [29]	Group 1: rTMS (n = 37) Group 2: control (n = 36)	Group 1: 68.62 ± 10.67 Group 2: 65.83 ± 8.45	Group 1: 14/23 Group 2: 11/25	ischemic stroke	within 7 days	ipsilesional M1 and DLPFC	10 Hz	80–90% RMT	3000	NIHSS, ADL(BI)	No adverse events.

FMA, Fugl-Meyer Assessment; RMT, resting motor threshold; FMA-UL, Fugl-Meyer Assessment-Upper Limb; NIHSS, National Institutes of Health Stroke Scale; ADL, Activities of Daily Living; BI, Barthel Index; mRS, modified Rankin Scale; MEP, Motor Evoked Potential; FMA-LL, Fugl-Meyer Assessment Lower Limb; CMCT, Central Motor Conduction Time; iTBS, Intermittent Theta Burst Stimulation; DLPFC, Dorsolateral Prefrontal Cortex; HF, high-frequency; LF, low-frequency.

For normally distributed variables: Data are presented as mean ± SD. For skewed/non-normally distributed variables: Data are presented as median (IQR) or median (range).

ment Upper Limb, FMA-UL) and lower limb (Fugl-Meyer Assessment Lower Limb, FMA-LL) subscales, as well as on activities of daily living (Barthel Index, BI), neurological deficit (National Institutes of Health Stroke Scale, NIHSS), disability (modified Rankin Scale, mRS), grip strength, and neurophysiological parameters. Our research aims to provide higher-quality, evidence-based support for motor function recovery in acute stroke patients through systematic review of rTMS effects on motor function, activities of daily living, and neurophysiological outcomes.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist in **Supplementary Material**) and was prospectively registered with PROSPERO (CRD42024597506). Due to word limit restrictions, for full details regarding the search strategy, inclusion/exclusion criteria, risk-of-bias assessment, data extraction, and statistical methods, please refer to the **Supplementary Methods** file.

3. Results

3.1 Search Results

After screening 2232 records with an additional 22 records identified from other sources and reviewing 180 full-text articles, 17 studies were eligible for inclusion in the analysis. The selection process is summarized in the PRISMA flowchart (Fig. 1).

3.2 Characterization of Included Studies

Table 1 (Ref. [13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29]) provides a comprehensive and concise synopsis of the key characteristics of the 17 studies encompassed within our rigorous analysis.

3.3 Risk of Bias

The risk of bias for the included randomized controlled trials (RCTs) and clinical controlled trials (CCTs) is summarized in Fig. 2. Overall, the studies demonstrated satisfactory performance regarding incomplete outcome data and selective reporting, with all studies rated as having a low risk of bias in these domains. For random sequence generation, 15 out of 17 studies were rated as having a low risk of bias. For allocation concealment, 11 studies were rated as having a low risk of bias, while 5 studies had an unclear risk, and 1 study demonstrated a high risk. In terms of blinding of participants and personnel, 8 studies were rated as having a low risk, while 9 were categorized as having an unclear risk. Regarding the blinding of outcome assessment, 15 studies were rated as having a low risk, and 2 studies were rated as unclear.

3.4 rTMS Improved the Neurological Deficits Assessed by FMA and NIHSS in Acute Stroke

In our meta-analysis, some studies reported the total FMA score, while others provided only upper-limb (FMA-UL) or lower-limb (FMA-LL) subscores. In our pooled analysis, rTMS treatment resulted in a significant increase in overall FMA scores (Hedges' g = 2.30, 95% CI: 1.45 to 3.14, $p < 0.01$) with a high degree of heterogeneity between studies (I^2 = 95.51%, $p < 0.01$). In detail, rTMS significantly increased FMA ($z = 4.05$, $p < 0.01$), FMA-LL ($z = 4.80$, $p < 0.01$), and FMA-UL ($z = 2.92$, $p < 0.01$) scores compared to the control group (Fig. 3A). The Galbraith plot showed that all points fell within the confidence limits except one study (Chen et al. 2021 [13]; **Supplementary Fig. 1A**). We deleted this study and conducted a meta-analysis on all studies again, and the results showed the heterogeneity of the studies were substantially reduced in overall FMA scores ($I^2 = 84.19\%$, $p < 0.01$). Notably, the I^2 for FMA-UL dropped dramatically from 97.63% to 0.00% following the exclusion of Chen et al. (2021) [13], suggesting that this study was likely the primary source of high heterogeneity. The dissymmetry of the funnel plot (**Supplementary Fig. 1B**) and Egger's test ($p < 0.01$) implied the possible existence of publication bias.

In our pooled analysis, rTMS treatment resulted in a significant reduction in NIHSS scores (Hedges' g = –1.24, 95% CI: –1.65 to –0.82, $p < 0.01$), indicating a substantial improvement in neurological function. The heterogeneity across studies was high (I^2 = 84.18%, $p < 0.01$), suggesting considerable variability in the effect sizes across different study designs and patient populations (Fig. 3B). The Galbraith plot indicated that all data points fell within the confidence limits except for one study (Khedr et al. 2010 [23]; **Supplementary Fig. 1C**). After excluding this outlier, the meta-analysis on the remaining studies showed a reduction in heterogeneity (I^2 = 71.21%, $p < 0.01$). The funnel plot assesses publication bias and reveals asymmetry (**Supplementary Fig. 1D**), suggesting the potential for bias. Egger's test for publication bias was significant ($p < 0.001$), confirming the presence of bias in the analyses. However, upon removing the study by Khedr et al. (2010) [23], Egger's test returned a non-significant result ($p = 0.16$), suggesting that this particular study's results or characteristics (e.g., its effect size, precision, or direction of findings) were a major contributor to the asymmetry in the funnel plot.

3.5 rTMS Enhanced Activities of Daily Living (ADL) Assessed by BI in Acute Stroke

The meta-analysis results demonstrate that rTMS treatment resulted in a significant improvement in the BI scores (Hedges' g = 2.65, 95% CI: 0.65 to 4.65, p = 0.01), suggesting a substantial enhancement in functional recovery. The heterogeneity across studies was high (I^2 = 98.74%, $p < 0.01$; Fig. 3C). The Galbraith plot indicated

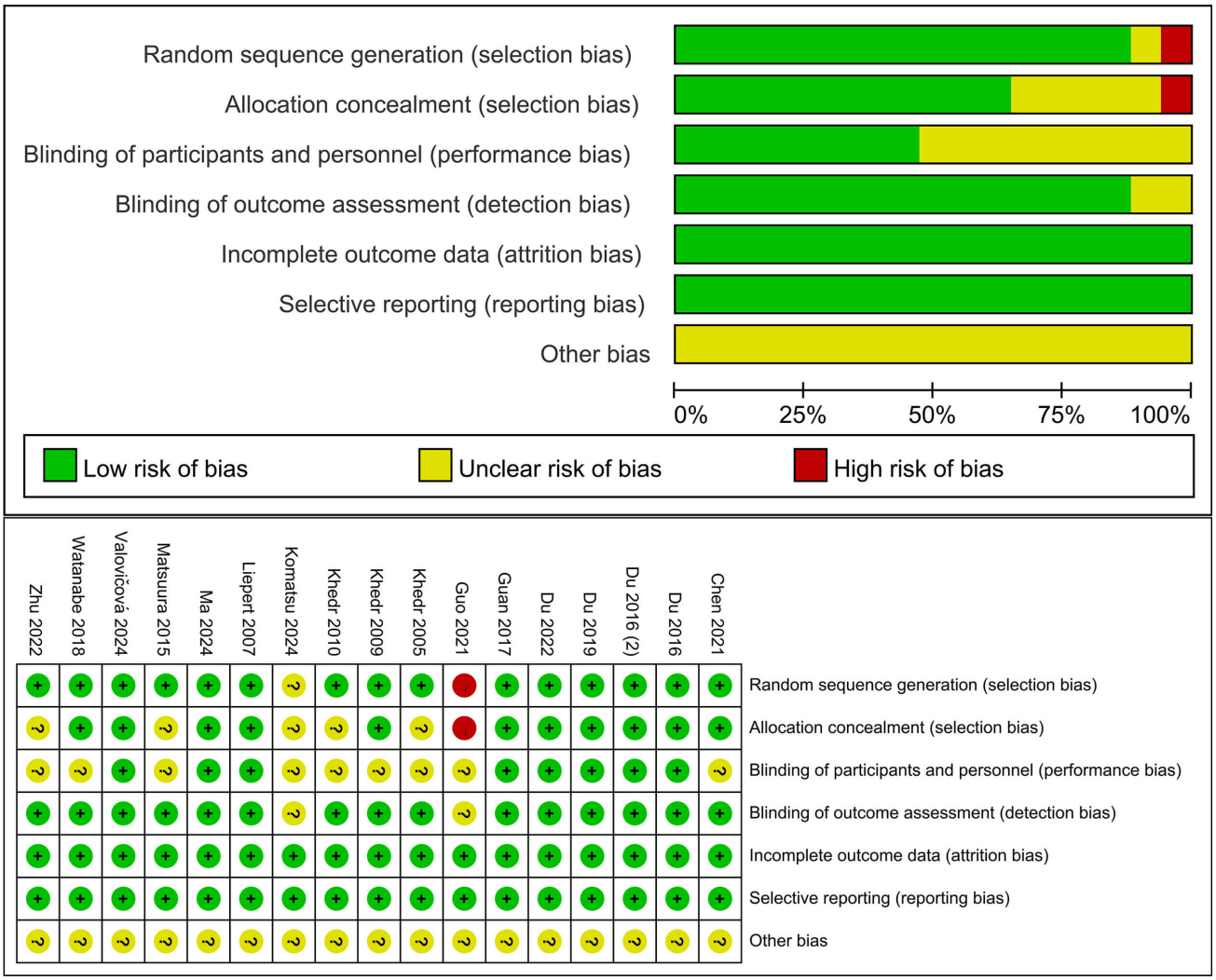

Fig. 2. Risk of bias in the included studies.

that most data points fell within the confidence limits except for one study (Chen et al. 2021 [13]; **Supplementary Fig. 1E**). When this outlier was removed, the analysis of the remaining studies demonstrated lower heterogeneity (I^2 = 0.00%, $p < 0.01$). We assessed potential publication bias using the funnel plot, which suggested a significant asymmetry (**Supplementary Fig. 1F**), indicating the presence of publication bias. The presence of such bias was confirmed by Egger's test ($p < 0.001$). However, upon removing the study by Chen et al. (2021) [13], the publication bias was no longer evident, and Egger's test returned a non-significant result ($p = 0.49$). The dramatic reduction in heterogeneity and publication bias indicates that the removed study (Chen et al. 2021 [13]) was a major outlier and the primary source of inconsistency among the included studies. Its exclusion yields a more homogeneous and unbiased body of evidence for synthesis.

3.6 rTMS Reduced Disability Assessed by mRS and Grip Strength in Acute Stroke

The analysis shows that rTMS resulted in a substantial decrease in disability (Hedges' g = –1.88, 95% CI: –3.02 to –0.74, $p < 0.01$; Fig. 4A), suggesting that rTMS contributed to better functional recovery in stroke patients. The heterogeneity across studies was high (I^2 = 94.23%, $p < 0.01$), indicating substantial variability between the included studies. The Galbraith plot shows that most studies fell within the confidence limits except for one study (Khedr et al. 2010 [23]; **Supplementary Fig. 2A**) deviated from the expected trend. Omitting the outlier led to a decrease in heterogeneity across the remaining studies (I^2 = 70.80%, $p < 0.01$).

In addition to evaluating the impact on mRS, the analysis also explored the effect of rTMS on grip strength. The results demonstrate that rTMS significantly improved grip strength in acute ischemic stroke patients, as indicated by a positive effect (Hedges' g = 0.87, 95% CI: 0.20 to 1.55, p = 0.01; Fig. 4B). Although the I^2 statistic indicates moderate to high heterogeneity (I^2 = 61.29%), the heterogeneity

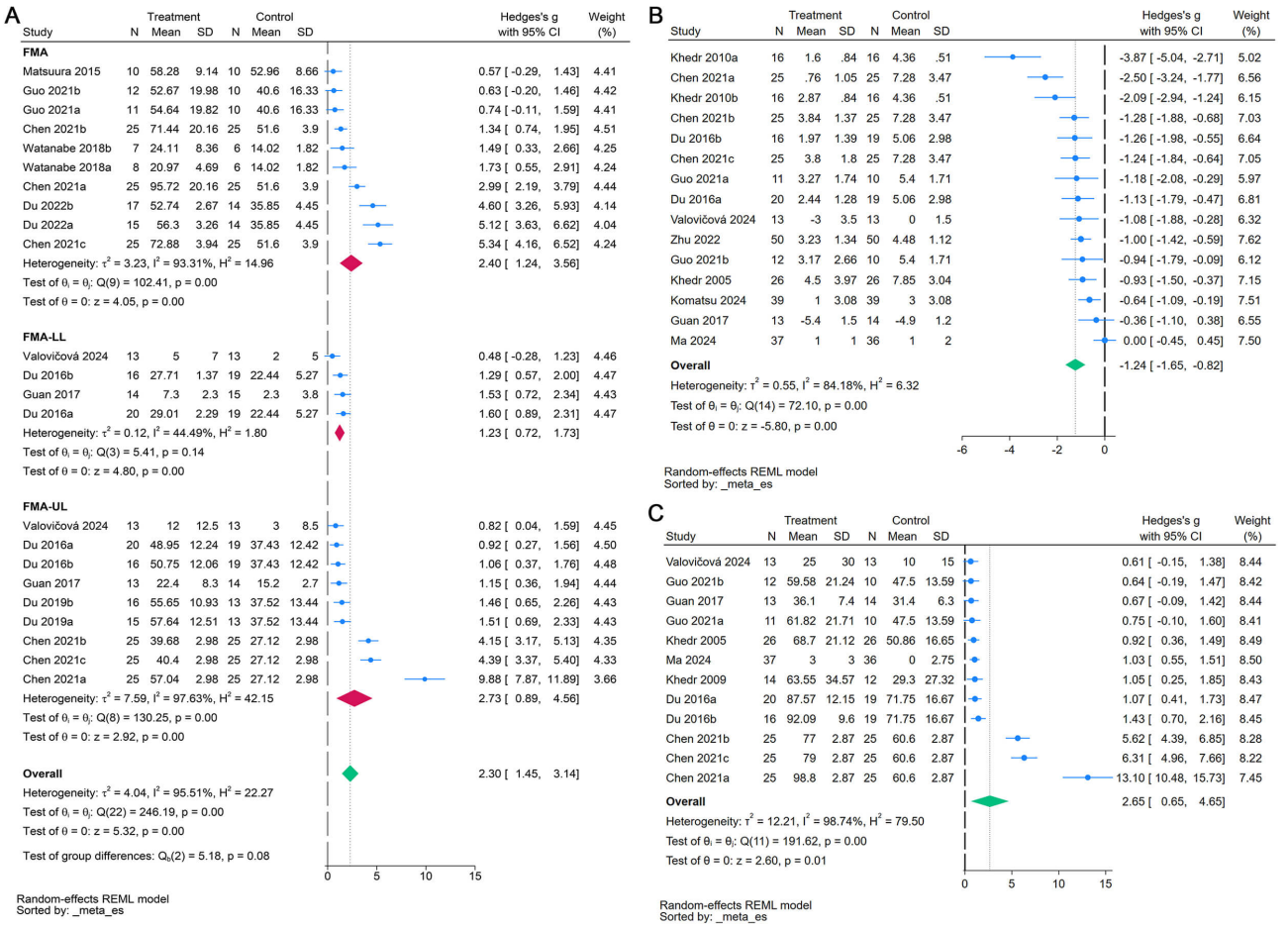

Fig. 3. The forest plot illustrates the overall impact of rTMS on FMA, NIHSS and BI in the acute phase of stroke. Forest plots under a random-effects model showed that rTMS treatment led to (A) a significant increase in FMA scores (indicating improved motor function), (B) a significant decrease in NIHSS scores (reflecting reduced neurological deficit), and (C) a significant increase in BI scores (suggesting better performance in activities of daily living).

test did not reach statistical significance ($p = 0.05$). Therefore, we cannot conclude that there is significant heterogeneity among the studies. The Galbraith plot highlights that all studies fit within the expected confidence limits, indicating that no outlier studies influenced our analysis (**Supplementary Fig. 2B**).

3.7 rTMS on MEP Amplitude in Acute Stroke

The meta-analysis revealed a significant improvement in MEP amplitude on the lesioned side of the brain following rTMS treatment. The results showed a positive effect (Hedges' g = 0.77, 95% CI: 0.52 to 1.02, $p < 0.01$; Fig. 4C), indicating that rTMS enhanced motor recovery by increasing corticospinal excitability on the affected side. No significant heterogeneity was observed among the studies ($I^2 = 30.76\%$, $p = 0.18$). The Galbraith plot shows that most studies fell within the confidence limits except for one study (Chen et al. 2021 [13]; **Supplementary Fig. 2C**). After removing the outlier, the meta-analysis showed that heterogeneity among the remaining studies was significantly reduced ($I^2 = 0.00\%$, $p < 0.01$), suggesting that it was the primary source of variability among the studies. We assessed potential publication bias through funnel plots (**Supplementary Fig. 2D**), and no significant asymmetry was observed. The Egger's test confirmed the absence of publication bias ($p = 0.698$) for lesioned sides. In contrast, rTMS did not show a significant effect on MEP amplitude on the nonlesioned side (Hedges' g = –0.22, 95% CI: –0.62 to 0.18, $p = 0.29$). The Galbraith plot indicates that the studies largely clustered near the regression line except for one study (Du et al. 2016 [16], **Supplementary Fig. 2E**).

3.8 rTMS on RMT in Acute Stroke

The meta-analysis revealed that rTMS significantly decreased RMT on the lesioned side of the brain, indicating an improvement in cortical excitability and motor function. The analysis showed a notable effect (Hedges' g = –1.13, 95% CI: –1.63 to –0.62, $p < 0.01$), suggesting that rTMS facilitated motor recovery on the affected side. The heterogeneity across studies was high ($I^2 = 79.01\%$, $p < 0.01$; Fig. 5A), which indicates variability in the treatment effects across different studies. The Galbraith plot shows that

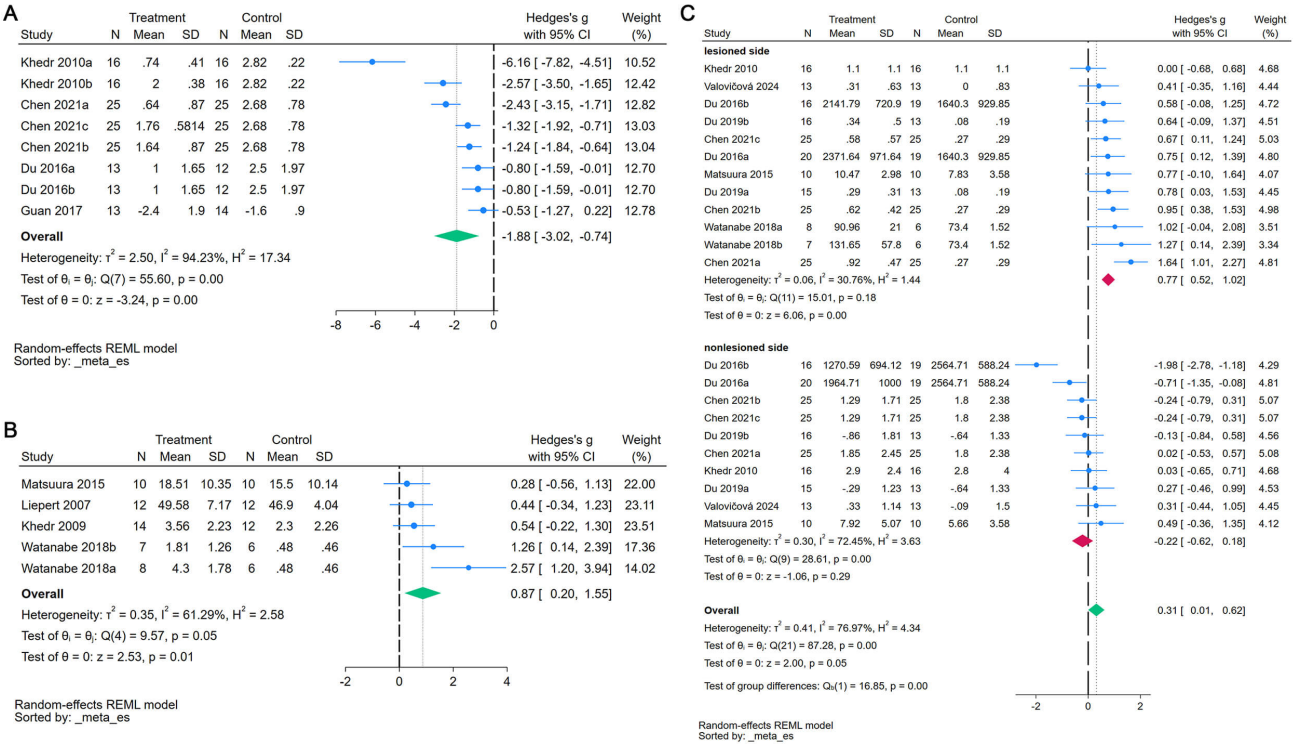

Fig. 4. The forest plot illustrates the overall impact of rTMS on the mRS, grip strength and MEP amplitude in the acute phase of stroke. As shown in the forest plots, rTMS demonstrated (A) a significant beneficial effect on functional outcome (mRS) and (B) a significant increase in grip strength. (C) For neurophysiological outcomes, rTMS significantly elevated MEP amplitude specifically on the lesioned hemisphere, with no significant change on the nonlesioned side.

all studies fall within the confidence limits, confirming the consistency of the result (**Supplementary Fig. 3A**). On the nonlesioned side, rTMS did not show a significant effect on resting motor threshold (RMT) (Hedges' g = 0.26, 95% CI: –0.14 to 0.66, $p = 0.20$). The Galbraith plot shows that all studies clustered near the regression line (**Supplementary Fig. 3B**).

3.9 rTMS on Central Motor Conduction Time (CMCT) in Acute Stroke

The meta-analysis revealed that rTMS did not significantly affect CMCT on either the lesioned side (Hedges' g = –0.41, 95% CI: –0.85 to 0.02, $p = 0.06$) or the nonlesioned side (Hedges' g = –0.19, 95% CI: –0.44 to 0.07, $p = 0.15$; Fig. 5B), suggesting no improvement in motor conduction on either side. The Galbraith plot shows that all studies clustered near the regression line (**Supplementary Fig. 3C,D**).

3.10 Safety of rTMS in the Acute Stroke

The safety profile of rTMS in the acute stroke phase was evaluated based on adverse event reporting from the included studies, as detailed in Table 1. Among the 17 studies, the majority explicitly reported on safety outcomes. No serious adverse events (SAEs) such as seizures or neurological deterioration attributable to the rTMS intervention were reported in any of the trials. The most commonly reported adverse events were transient and mild, including headache and scalp discomfort or tingling sensation at the stimulation site at the beginning of sessions, which typically resolved spontaneously or with simple measures. The incidence of these minor events was low and comparable between the real rTMS and sham-control groups in studies that reported them. Overall, the evidence from the included studies indicates that rTMS, when applied within the reported parameters and to appropriately selected acute stroke patients, is a safe intervention with a favorable risk profile.

3.11 Subgroup Analysis

3.11.1 Ipsilesional HF-rTMS Versus Contralesional LF-rTMS

A subgroup analysis was conducted comparing the effects of contralesional LF-rTMS and ipsilesional HF-rTMS to evaluate the impact of stimulation location and frequency on various stroke recovery outcomes.

Both stimulation locations significantly improved FMA scores, with ipsilesional HF-rTMS showing a stronger effect ($z = 4.56$, $p < 0.01$) compared to contralesional LF-rTMS ($z = 3.66$, $p < 0.01$). Both groups also demonstrated significant reductions in NIHSS scores (ipsilesional HF-rTMS: $z = –4.32$, $p < 0.01$; contralesional LF-rTMS: $z = –5.73$, $p < 0.01$).

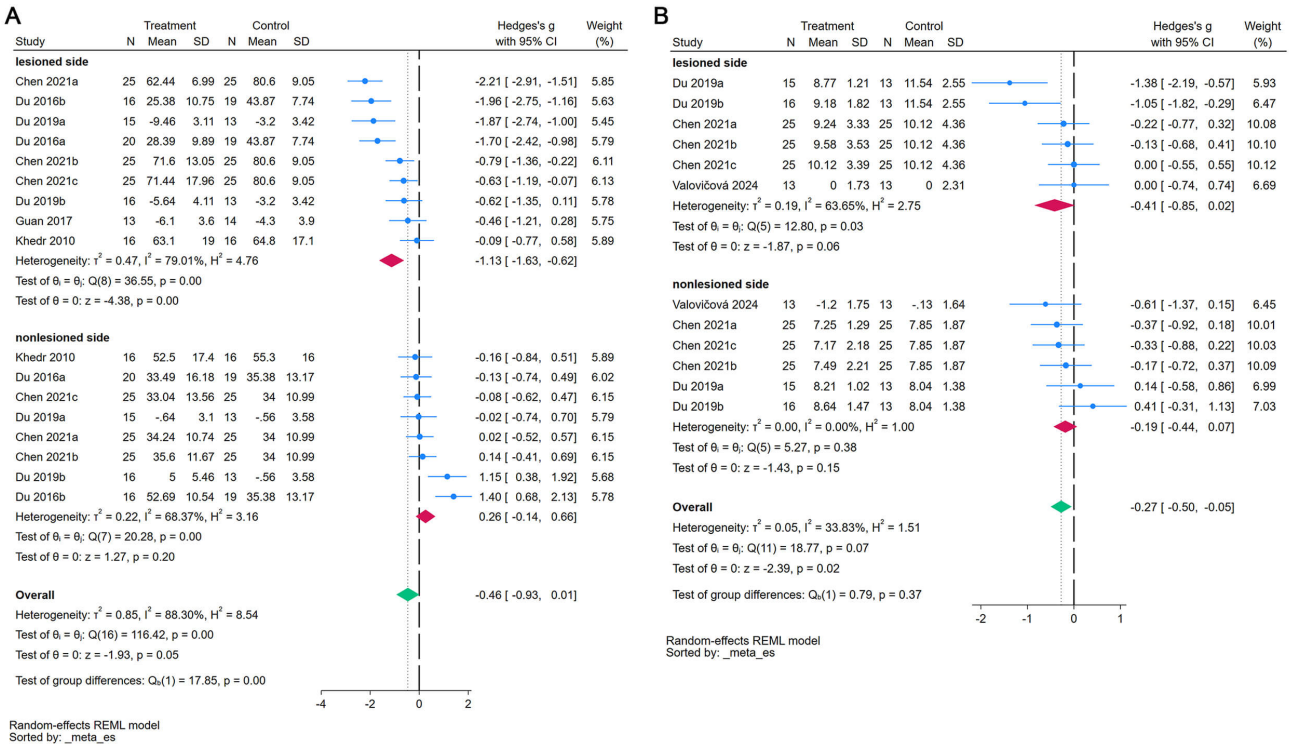

Fig. 5. The forest plot illustrates the overall impact of rTMS on RMT and CMCT in the acute phase of stroke. (A) The forest plot shows the effect of rTMS on RMT for both the lesioned and nonlesioned sides of the brain. The pooled results indicate a significant decrease on the lesioned side, whereas no significant effect was observed on the nonlesioned side. (B) The forest plot displays the effect of rTMS on CMCT for both the lesioned and nonlesioned sides of the brain. Individually, neither side shows a significant effect.

Regarding the BI, the improvements were significant only in the ipsilesional HF-rTMS group ($z = 2.56$, $p = 0.01$), while contralesional LF-rTMS did not reach statistical significance ($z = 1.57$, $p = 0.12$). For motor evoked potential (MEP) amplitude, both groups showed improvements (ipsilesional HF-rTMS: $z = 3.89$, $p < 0.01$; contralesional LF-rTMS: $z = 4.26$, $p < 0.01$). Both groups also showed significant reductions in RMT, with similar effects (ipsilesional HF-rTMS: $z = –2.84$, $p < 0.01$; contralesional LF-rTMS: $z = –2.43$, $p = 0.01$). Finally, for the mRS, contralesional LF-rTMS ($z = –4.52$, $p < 0.01$) had a stronger effect compared to ipsilesional HF-rTMS ($z = –2.22$, $p = 0.03$; Table 2).

3.11.2 Different Intensity of rTMS

A subgroup analysis was conducted to compare the effects of different stimulation intensities (subthreshold, suprathreshold, and threshold) on various stroke recovery outcomes.

The effect of stimulation intensity on FMA score improvement was level-dependent. The enhancement was marked by a significant and strongest effect under suprathreshold stimulation ($z = 4.62$, $p < 0.01$), a significant effect under subthreshold stimulation ($z = 3.49$, $p < 0.01$), but no significant difference under threshold stimulation ($z = 1.87$, $p = 0.06$). Regarding the NIHSS, subthreshold stimulation demonstrated the most significant improvement ($z = –3.97$, $p < 0.01$), followed by threshold stimulation ($z = –3.11$, $p < 0.01$). Suprathreshold stimulation showed a non-significant effect ($z = –1.58$, $p = 0.11$; Table 2).

3.12 Quality of Evidence

The detailed quality assessments for each outcome are presented in Table 3. Out of 8 outcomes assessed, 6 were rated as low quality, 1 as moderate quality, and 1 as high quality. The low-quality outcomes included the FMA, NIHSS, BI, mRS, Grip strength, and CMCT on the lesioned side. These outcomes were downgraded due to factors such as inconsistency across studies, publication bias, and imprecision in the data. It should be noted that subjective scales (e.g., FMA, NIHSS, BI, mRS, and grip strength) are inherently less reliable than objective measures like MEP and RMT, which further contributed to the lower quality ratings. The moderate-quality outcome was the RMT on the lesioned side, which showed some inconsistency across studies but remained relatively robust overall. The only outcome rated as high quality was the MEP amplitude on the lesioned side, which demonstrated consistent results across studies with minimal risk of bias.

4. Discussion

Our systematic review and meta-analysis evaluated 17 rigorous RCTs and CCTs. Results demonstrated that rTMS

Table 2. Subgroup analysis of rTMS' effect across ipsilesional HF versus contralesional LF and different stimulation intensities.

Comparison	Subgroup	Datasets	Patients	SMD	95% CI	I^2	*p*-value	Z
Ipsilesional HF versus contralesional LF	FMA							
	ipsilesional HF	12	378	1.68	[0.96, 2.41]	89.39%	<0.001	4.56
	contralesional LF	8	285	2.27	[1.06, 3.49]	93.85%	<0.001	3.66
	NIHSS							
	ipsilesional HF	11	530	–1.16	[–1.68, –0.63]	87.23%	<0.001	–4.32
	contralesional LF	3	107	–1.18	[–1.58, –0.78]	0.00%	<0.001	–5.73
	BI							
	ipsilesional HF	8	314	1.42	[0.33, 2.50]	94.66%	0.01	2.56
	contralesional LF	3	107	2.75	[–0.68, 6.19]	97.58%	0.12*	1.57
	MEP amplitude							
	ipsilesional HF	6	189	0.64	[0.32, 0.96]	18.10%	<0.001	3.89
	contralesional LF	5	147	0.71	[0.38, 1.03]	0.00%	<0.001	4.26
	RMT							
	ipsilesional HF	5	176	–0.96	[–1.62, –0.30]	77.26%	<0.001	–2.84
	contralesional LF	3	114	–1.04	[–1.88, –0.20]	77.44%	0.01	–2.43
	mRS							
	ipsilesional HF	5	166	–2.17	[–4.09, –0.25]	96.18%	0.03	–2.22
	contralesional LF	2	75	–1.12	[–1.61, –0.64]	2.91%	<0.001	–4.52
Subthreshold stimulation versus threshold stimulation versus suprathreshold stimulation	FMA							
	subthreshold stimulation	6	213	1.72	[0.75, 2.68]	88.89%	<0.001	3.49
	threshold stimulation	4	109	1.90	[–0.09, 3.90]	94.99%	0.06*	1.87
	suprathreshold stimulation	2	56	1.34	[0.77, 1.91]	0.00%	<0.001	4.62
	NIHSS							
	subthreshold stimulation	6	361	–0.83	[–1.24, –0.42]	70.37%	<0.001	–3.97
	threshold stimulation	2	58	–1.57	[–2.57, –0.58]	65.41%	<0.001	–3.11
	suprathreshold stimulation	3	111	–1.67	[–3.75, 0.41]	95.29%	0.11*	–1.58

SMD, Standardized Mean Difference. *No statistical significance was observed in this subgroup.

significantly outperformed control interventions in improving motor function among acute stroke patients, as measured by the FMA, grip strength, and the NIHSS. Improvements were also observed in activities of daily living, assessed via the BI and mRS, as well as neurophysiological parameters including ipsilesional MEP amplitude and RMT, with minimal adverse effects reported. Notably, subgroup analyses revealed that ipsilesional HF-rTMS effectively improved BI scores, while contralesional LF-rTMS showed no statistically significant BI improvements. Additionally, different intensities (subthreshold and suprathreshold) of ipsilesional HF-rTMS demonstrated comparable effects on FMA scores in early stroke patients. Both subthreshold and threshold rTMS effectively improved NIHSS scores, while suprathreshold stimulation showed no significant NIHSS improvements.

The International Federation of Clinical Neurophysiology's "Evidence-based guidelines on the therapeutic use of rTMS" reviewed literature from 2014 to 2018 [30]. For post-stroke motor dysfunction in the subacute phase, clinical recommendations included LF-rTMS of contralesional M1 (Level A: definite efficacy) and HF-rTMS of ipsilesional M1 (Level B: probable efficacy). For chronic stroke, LF-rTMS of contralesional M1 was recommended with Level C evidence (possible efficacy). No definitive recommendations could be established for rTMS treatment in acute stroke, consistent with conclusions from several recent systematic reviews and meta-analyses [31,32,33]. Our meta-analysis demonstrates that rTMS shows significant benefits compared to sham stimulation in acute stroke patients. The advantages of rTMS treatment in the acute phase extend beyond motor function improvements to include enhanced ADL and neurophysiological parameters. Extensive research highlights the necessity of initiating stroke rehabilitation during the acute phase rather than waiting until the chronic phase [11,34]. The acute post-stroke recovery period is considered a critical therapeutic window [35,36], during which intervention is believed to more effectively provide neuroprotection and repair, generating enhanced neuroplasticity [37] that promotes motor function recovery—a key factor in achieving optimal rehabilitation outcomes [38,39]. A series of animal studies demonstrate that acute-phase rTMS application improved neurological function and reduced lesion volume in ischemic stroke rats [40,41,42]. Fujiki et al. [43] found that rTMS reduced post-stroke hippocampal neuronal death. Motor function improvement, infarct volume reduction, and neuronal protection are attributed to rTMS's non-pharmacological anti-

Table 3. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) summary of findings of quality of evidence.

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk		
	Control	rTMS		
FMA		The mean FMA in the intervention groups was 2.30 standard deviations higher (1.45 to 3.14 higher)	763 (23 comparisons)	⊕⊕⊖⊖ low[1]
NIHSS		The mean NIHSS in the intervention groups was 1.24 standard deviations lower (1.65 to 0.82 lower)	687 (15 comparisons)	⊕⊕⊖⊖ low[1]
BI		The mean BI in the intervention groups was 2.65 standard deviations higher (0.65 to 4.65 higher)	471 (12 comparisons)	⊕⊕⊖⊖ low[1]
mRS		The mean mRS in the intervention groups was 1.88 standard deviations lower (3.02 to 0.74 lower)	291 (8 comparisons)	⊕⊕⊖⊖ low[1]
Grip strength		The mean grip strength in the intervention groups was 0.87 standard deviations higher (0.2 to 1.55 higher)	97 (5 comparisons)	⊕⊕⊖⊖ low[1]
MEP amplitude on lesioned side		The mean MEP on lesioned side in the intervention groups was 0.77 standard deviations higher (0.52 to 1.02 higher)	386 (12 comparisons)	⊕⊕⊕⊕ high[1]
RMT on lesioned side		The mean RMT on lesioned side in the intervention groups was 1.13 standard deviations lower (1.63 to 0.62 lower)	340 (9 comparisons)	⊕⊕⊕⊖ moderate[1]
CMCT on lesioned side		The mean CMCT in lesioned side in the intervention groups was 0.41 standard deviations lower (0.85 lower to 0.02 higher)	233 (6 comparisons)	⊕⊕⊖⊖ low[1]

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[1]GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

apoptotic effects in perilesional regions, thus ameliorating motor dysfunction caused by brain injury [44,45,46,47]. In *in vitro* ischemia models, rTMS has been shown to induce neuroprotective extracellular signal-regulated kinase 1/2 and c-Fos pathways in neuron-glial cortical cultures, reducing neuronal cell death and increasing synaptic markers [48]. In Bai et al.'s [49,50] rTMS-related research on early stroke patients, significantly elevated serum brain-derived neurotrophic factor (BDNF) levels were observed in the experimental group receiving TMS intervention compared to controls, suggesting rTMS may promote functional recovery by enhancing neurogenesis and activating BDNF signaling pathways. Notably, the intervention time window across studies (from a few days to two weeks post-stroke) indeed spans the early and later sub-phases of the acute period. Neuroplasticity and molecular pathways involved in inflammation and repair evolve rapidly during this phase. Early intervention (e.g., within 3 days) may target different pathophysiological processes (e.g., mitigating secondary damage, regulating the microglia- and astrocyte-mediated inflammatory response [42,44]), while later intervention (e.g., 1–2 weeks) may focus more on functional reorganization and connectivity remodeling.

Our subgroup analysis revealed noteworthy findings. Firstly, ipsilesional HF-rTMS significantly improved BI scores, while contralesional LF-rTMS showed no statistically significant improvements. This suggests that ipsilesional HF-rTMS holds greater potential for enhancing activities of daily living, including upper and lower limb functions—a finding consistent with a recent meta-analysis demonstrating the superior efficacy of HF-rTMS over LF-rTMS [51]. The therapeutic mechanisms may stem from

direct modulation of the lesioned primary motor cortex (M1). rTMS is believed to induce neuroplasticity in neurons within the damaged area, enhance connectivity between cortical neurons, and transiently increase cerebral blood flow, thereby promoting functional reorganization of surviving neurons during treatment to facilitate motor recovery [52,53]. From the perspective of neuronal reorganization, HF-rTMS may be more suitable than LF-rTMS in the early post-stroke phase. Xu et al. [54] found that, compared with healthy controls, resting-state functional connectivity (rsFC) between the contralesional primary sensorimotor cortex and bilateral primary sensorimotor cortices was initially decreased in patients with subcortical stroke. It then gradually increased and eventually returned to normal levels at one year post-stroke. Furthermore, the dynamic changes in interhemispheric rsFC between the bilateral primary sensorimotor cortices were positively correlated with Motricity Index (MI) scores, implying that the contralesional hemisphere may play a more significant role in spontaneous recovery during the subacute phase rather than the early phase. Concurrently, early-phase activation of the ipsilesional hemisphere was also associated with better motor recovery in hemiplegic patients [55]. These results support the rationale for applying HF-rTMS to the lesioned hemisphere in early stages. Studies utilizing task-based fMRI have reported that inhibitory rTMS exerts far weaker effects on contralesional M1 activation compared to excitatory rTMS's impact on ipsilesional M1. Furthermore, ipsilesional motor cortex activity showed significant correlations with motor function both immediately post-intervention and at 3-month follow-up [17]. Resting-state fMRI findings additionally revealed that compared to LF-rTMS applied to the contralesional M1, HF-rTMS contributed more substantially to functional connectivity reconstruction within perilesional motor networks, enabling patients to achieve greater motor recovery [27]. Animal experiments demonstrated that HF-rTMS, compared to LF-rTMS stimulation, better regulates neurotransmitters and induces higher postsynaptic density, thereby more effectively promoting post-stroke neural repair [56]. Therefore, applying HF magnetic stimulation to the lesioned hemisphere in acute stroke patients may offer superior therapeutic benefits.

Regarding TMS stimulation intensity, our analysis revealed varying protocols across studies. Stimulation intensity is a critical parameter influencing TMS efficacy, with considerable variation across studies. Higher intensities may increase adverse event risk and reduce patient compliance, while insufficient intensities could compromise TMS outcomes [57]. Huang and Rothwell [58] evaluated different threshold stimulation intensities, finding 80% threshold intensity optimal for modulating corticospinal excitability. Furthermore, Chung et al. [59] investigated varying threshold intensities on neurophysiological and prefrontal cortical behavior, demonstrating optimal neurophysiological and working memory effects at 75% RMT. These findings suggest that higher intensities do not necessarily correlate with better cortical excitability modulation, and subthreshold or threshold stimulation intensities may yield comparable benefits [60]. The in vitro cellular study revealed that although appropriate-intensity low-frequency rTMS promoted neuronal survival and upregulated the expression of iron-containing enzymes, excessive high-intensity rTMS exertd neurotoxic effects, impairing neuronal morphology, reducing neuronal viability, and altering the expression of iron-containing enzymes, thereby disrupting neuronal and synaptic structural homeostasis [61]. In cultured hippocampal neurons, high-intensity low-frequency magnetic stimulation produces detrimental structural alterations, including reduced dendritic-axonal arborization, decreased synapse density and thinning of postsynaptic density [62]. These findings raise concerns regarding excessive stimulation intensity when applying rTMS under brain-injured conditions. Consequently, threshold or subthreshold stimulation intensities may represent more appropriate therapeutic parameters for acute stroke patients.

Our grading of recommendations, assessment, development and evaluation (GRADE) evidence assessment revealed varying certainty levels across outcome measures. The MEP amplitude from the affected hemisphere demonstrated high-quality evidence, whereas the RMT of the lesioned hemisphere showed moderate-quality evidence. Notably, clinical assessment scales (FMA, NIHSS, BI) and functional measurements (grip strength) were predominantly classified as low-quality evidence (where subsequent research may modify current conclusions). This hierarchical grading likely reflects the association between neurophysiological biomarkers in the first dorsal interosseous (FDI) motor cortex of the affected hemisphere and rTMS mechanisms [63,64]. The superior evidence quality for MEP and RMT measurements may be attributed to their high precision as direct neurophysiological biomarkers of corticospinal excitability evolution during recovery, rather than as primary clinical endpoints [65]. Notably, corticospinal excitability changes measured through the first dorsal interosseous (FDI) also represent motor cortical reorganization, reflecting a degree of neural plasticity [66]. TMS-derived MEP can serve as a complementary prognostic biomarker beyond conventional clinical assessments. In patients with first-ever middle-cerebral-artery stroke and initial hand palsy, early MEP amplitude from the affected FDI improves the prediction of 4-month hand motor outcome when incorporated into multivariate models together with NIHSS scores [67]. Prospective follow-up studies further indicate their utility as early prognostic indicators for motor function recovery in acute stroke patients with hemiplegia [68]. Conversely, the limitations of clinical scales may stem from multiple factors: First, inherent inaccuracies and biases arising from assessors' subjective perceptions [69]. Second, ceiling effects that may obscure

true therapeutic outcomes, particularly prevalent in acute-phase patients [70,71]. Third, high-quality GRADE rating for MEP amplitude primarily applies to patients with mild-to-moderate impairment. We explicitly acknowledge that for patients with severe stroke and absent MEPs, evidence regarding the efficacy and neurophysiological effects of rTMS is scarce.

5. Limitation

Analytically, unstratified pathological subtypes, demographic variables, and lesion topology heterogeneity [30,72], compounded by insufficient statistical power from limited sample sizes [73], collectively introduce confounding factors. Future research should further refine patient characteristics. For instance, lacunar infarcts differ from non-lacunar strokes in their pathophysiological mechanisms and clinical prognosis [74]. However, the studies included in this review generally lacked subgroup analysis data based on stroke etiology. Furthermore, sex-related disparities exist in stroke risk and prognosis. Notably, oldest-old women with acute ischemic stroke constitute a high-risk subgroup with poor in-hospital outcomes [75]. A recent imaging study systematically demonstrated that, due to differences in skull morphology (e.g., thinner frontal and occipital bones), females have a significantly shorter scalp-to-cortex distance, leading to systematically stronger induced electric fields when receiving the same nominal stimulus intensity [76]. Unfortunately, none of the studies in our review considered or controlled for this anatomical variable, which is a major limitation of the existing evidence base. Most of the included primary studies likely did not systematically report or stratify patients based on whether they received reperfusion therapies (intravenous thrombolysis or mechanical thrombectomy). These treatments, by rapidly restoring blood flow, profoundly alter the acute pathophysiological environment and neuroplasticity potential, potentially acting as strong effect modifiers. Failure to account for this factor makes it impossible to discern to what extent the observed rTMS effects are independent of or synergistic with reperfusion therapies. This limits the generalizability of our findings across the broad acute stroke population, which includes varying proportions of patients receiving reperfusion. Mechanistically, although several studies have linked BDNF-Val66Met polymorphism to rTMS-induced neuroplastic changes and clinical outcomes, conflicting clinical observations and high risk of bias across existing studies prevent definitive causal inference connecting modulated synaptic plasticity to inter-individual variability in rTMS response [77,78]. Critical methodological variations, including heterogeneity in stimulation parameters (frequency, intensity, pulse count), outcome measures, post-intervention intervals, and non-standardized data processing [79,80], further exacerbate interpretation challenges. Additionally, our FMA analysis pooled total FMA, FMA-UL, and FMA-LL scores, which may have included repeated measurements from the same participants. Moreover, some multi-arm studies reused the same control group across multiple comparisons, potentially leading to an overestimation of sample size and precision. Therefore, readers should interpret the pooled FMA results with caution.

6. Conclusions

Despite certain limitations, our study confirms that rTMS is a safe and effective approach for improving post-stroke motor function and ADL during the acute phase. Preliminary evidence suggests that HF stimulation of the lesioned hemisphere at or below the motor threshold may yield superior therapeutic effects for patients. However, large effect sizes as indicative of the potential efficacy of rTMS in the acute phase, they should be viewed with caution. The determination of optimal parameters and development of feasible protocols require larger-scale, methodologically congruent trials. Furthermore, the design of such protocols must account for the practical challenges of implementing rTMS in acute stroke units. These challenges include managing patient-specific factors such as impaired consciousness, agitation, or unstable vital signs, and coordinating treatment timing with urgent diagnostic procedures, pharmacological therapies (e.g., thrombolysis or antiplatelets), and continuous patient monitoring. Future research should prioritize multicenter, large-sample, standardized neuronavigated double-blind randomized controlled studies, with an enhanced focus on molecular biomarker testing and the application of individualized precision targeting. These advancements are critical for establishing effective rTMS intervention strategies to address post-acute stroke motor dysfunction. Furthermore, future explorations could extend to the following directions: (1) integrating neuroimaging (e.g., fMRI, DTI) for individualized target localization and treatment response prediction; (2) exploring combined application models of rTMS with other rehabilitation technologies (e.g., robot-assisted training, virtual reality); (3) identifying biomarkers (e.g., genetic, serum molecular markers) predictive of rTMS response; (4) conducting efficacy studies targeting specific stroke subpopulations (e.g., specific stroke subtypes, very old patients); and (5) performing longer-term follow-ups to assess the sustained impact of rTMS on functional recovery.

Abbreviations

ADL, Activities of Daily Living; BI, Barthel Index; BDNF, Brain-Derived Neurotrophic Factor; CCTs, Clinical Controlled Trials; CMCT, Central Motor Conduction Time; CI, Confidence Interval; cTBS, Continuous Theta Burst Stimulation; DLPFC, Dorsolateral Prefrontal Cortex; DTI, Diffusion Tensor Imaging; FMA, Fugl-Meyer Assessment; FMA-LL, Fugl-Meyer Assessment Lower Limb; FMA-UL, Fugl-Meyer Assessment Upper Limb; fMRI, Functional Magnetic Resonance Imaging; GRADE, Grading of

Recommendations, Assessment, Development and Evaluation; HF-rTMS, High-Frequency Repetitive Transcranial Magnetic Stimulation; iTBS, Intermittent Theta Burst Stimulation; LF-rTMS, Low-Frequency Repetitive Transcranial Magnetic Stimulation; M1, Primary Motor Cortex; MEP, Motor Evoked Potential; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, Randomized Controlled Trials; RMT, resting motor threshold; rTMS, Repetitive Transcranial Magnetic Stimulation; SD, Standard Deviation; SMD, Standardized Mean Difference; SRRR, Stroke Recovery and Rehabilitation Roundtable; TMS, Transcranial Magnetic Stimulation.

Availability of Data and Materials

The data are available from the corresponding authors upon reasonable request.

Author Contributions

LL contributed to Conceptualization, Supervision, and Writing (original draft, review & editing); ML and HL were responsible for Investigation and Data curation; GY and CG contributed to Validation, and Writing (review & editing); YW and XJ were involved in study conception, overall experimental design and critical revision of the manuscript; XD contributed to Visualization and Investigation; XL contributed to Visualization and Formal analysis; SP contributed to Visualization and Methodology; JM contributed to Visualization and Resources. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN49076.

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